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Current epidemiology, risk factors, classification and pathophysiology in central serous chorioretinopathy

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ABSTRACT

CSCR is one of the important posterior segment diseases that threaten vision in middle-aged men. While the incidence in men is 9.9 per 100,000, it is 1.7 per 100,000 in women. Fellow eyes of patients with CSCR are usually asymptomatic. CSCR can be acute, recurrent, or chronic. Many risk factors for CSCR have been identified, such as genetic, environmental, drug, and other diseases. Optical coherence tomography, fundus autofluorescence, fundus fluorescein angiography, and indocyanine green angiography are used for diagnosis.

Keywords: Central serous chorioretinopathy, classification, epidemiology, pathophysiology, risk factors

INTRODUCTION

The term central serous chorioretinopathy (CSCR) was first used by Gass in 1967.[1] CSCR is one of the important posterior segment diseases that threaten vision in middle-aged men. The most common retinal problems that cause vision loss are age-related macular degeneration, diabetic retinopathy, branch retinal vein occlusion, and CSCR, respectively.[2]

Clinical findings of CSCR include localized neurosensory retinal (NSR) detachment (**Figure 1**, **2**) and retinal pigment epithelium (RPE) detachment (**Figure 2**). There is also choroidal thickening, excessive vascular permeability and venous overload.[3,4] Even if the subretinal fluid is reabsorbed in CSCR, recovery in visual acuity takes longer. Although these detachments are usually located within the temporal arcades, they can also be located outside the temporal arcades. Serous detachments occurring outside the temporal arcades are usually asymptomatic. These asymptomatic eyes are usually the fellow eyes of patients with CSCR. In addition, close relatives of patients with CSCR may also have asymptomatic CSCR.[5] Therefore, the prevalence of CSCR may be higher than the known. While bilaterality is reported as 4% at the first diagnosis, this rate increases to 40% in the follow-ups, and it is emphasized as bilateral asymmetric involvement in chronic cases.[6,7] While CSCR has a good visual prognosis in the acute phase, the visual prognosis is poor when chronicity and diffuse retinal pigment epitheliopathy develops.[2]

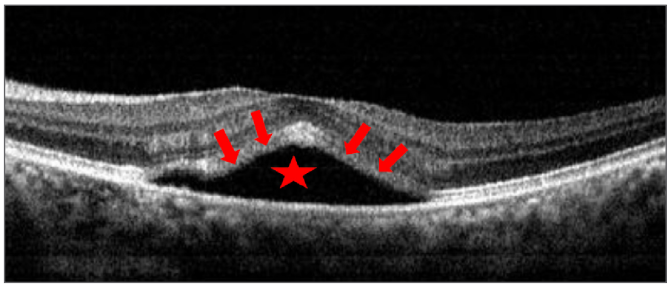

Figure 1. Neurosensorial retinal detachment (red arrows) and subretinal fluid (asterisk) on OCT imaging

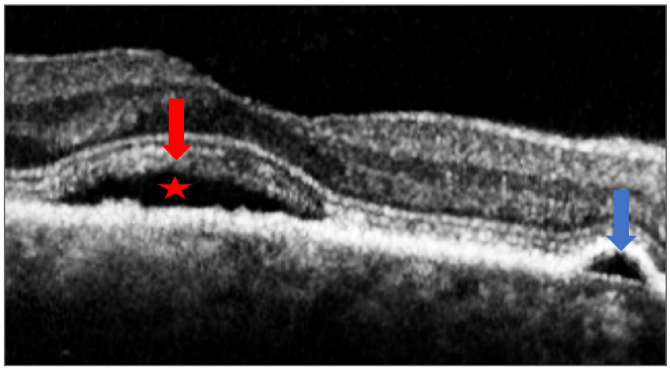

Figure 2. Neurosensorial retinal detachment (red arrows), subretinal fluid (asterisk) and RPE detachment (blue arrow) on OCT imaging

Although acute CSCR may be easier to diagnose when presenting to the clinic, chronic CSCR findings may be difficult to diagnose as they may be similar to age-related macular degeneration. In cases where it is difficult to diagnose, spectral domain optical coherence tomography (SD-OCT) helps us in the diagnosis by enabling us to better visualize the choroid.

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CSCR may be seen with increased or normal choroidal thickness. The outer segments of the photoreceptors at the leakage point corresponding to the region of the RPE detachment are observed an eroded appearance. In fundus autofluorescence (FAF) imaging in the region of NSR detachment, the outer segments of photoreceptors that fail to phagocytize are observed as spots with increased reflectance. Gravitational tracks are observed as hypo-autofluorescence in FAF (**Figure 3**). Fluorescein angiography (FFA) shows increased fluorescence due to RPE degeneration (**Figure 4**). Indocyanine green angiography (ICGA) shows dilated choroidal vessels, increased permeability, and late hypercyanecence. In enhanced depth imaging (EDI)-OCT, there is the elevation of the RPE just above the dilated choroidal vessels. There is increased reflectance in the walls of the choroidal vessels.

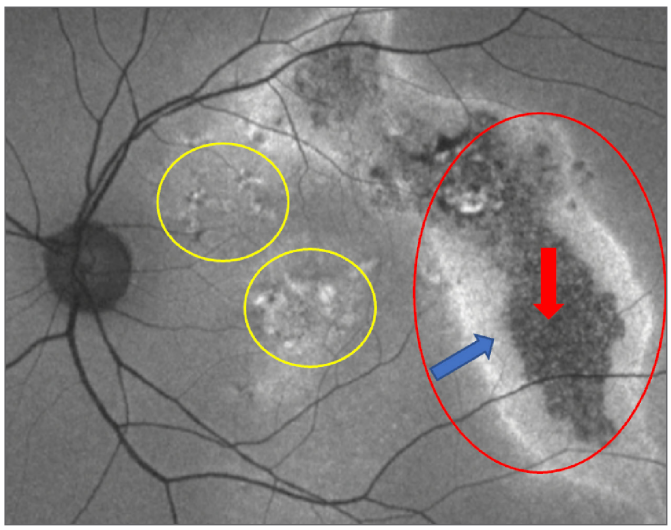

Figure 3. Hypoautofluorescence appearence of RPE (red arrows), hyperautofluorescence appearence of RPE (blue arrow), gravitational track (red circle) and RPE changing (yellow circles) on FAF imaging

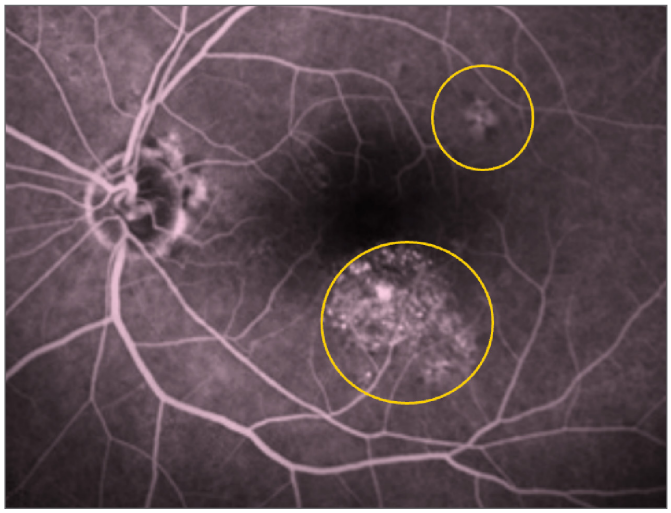

Figure 4. RPE changing (yellow circles) on FFA imaging

EPIDEMIOLOGY

72-88% of patients are male.[8,9] While the incidence in men is 9.9 per 100,000, it is 1.7 per 100,000 in women.[7] In the American data, the incidence of CSCR was stated as 23.4 per 100,000 men and 9.6 per 100,000 women.[10] CSCR is 6 times more common in men. While the classic acute form of CSCR is observed in young men, the atypical chronic form is more common in older women.[7] It has been shown that the significantly higher incidence of CSCR in men compared to women is valid only in the younger age group.[11] Although it is mainly a middle-aged disease, it can also be seen in children and those over 60 years of age.[12,13]

Reported more frequently in Asians, Caucasians, and Hispanics.[14] In addition, the amount of subretinal fluid in serous NSR detachment is higher in Asians.[15] CSCR in Asians is bilateral, multifocal, and has a poor prognosis.[16] In African-Americans, CSCR is less common but has a worse prognosis.[17] Visual acuity in African-Americans is lower at baseline and follow-up compared to the white population.[17]

Classification

While 51% of untreated CSCR cases resolve after the first attack, 49% become complicated.[18] CSCR can be acute, recurrent, or chronic.

1. **Acute CSCR:** Typical acute CSCR is characterized by symptoms and/or retinal detachment lasting less than 6 months and focal leaks on FFA. In the acute form, relative central scotoma, blurred vision, metamorphopsia, dyschromatopsia, micropsia, and decreased contrast sensitivity occur in patients due to subretinal fluid formed in the macular region. There are RPE changes, pigmentary epithelial detachment (PED), and leakage at the RPE level in the area of subretinal fluid. Subretinal fluid usually dissolves within 4-6 months. Other symptoms also improve without sequelae with the improvement of the findings. In some patients, a decrease in visual acuity, decrease in light sensitivity, color discrimination defect, and ERG changes may occur due to damage to the outer segments of photoreceptors.[19,20]
2. **Inactive CSCR:** The patient has a history of acute CSCR, but there is no other finding.
3. **Recurrent CSCR:** Patients who have had more than one attack are in this group. In CSCR, 1/3 of the cases develop relapse, and 50% of them relapse within the first year. Patients in this group appear in two ways.
   a. **Recurrent remission:** These are cases in which detachment and symptoms completely regressed after recurrent attacks. Also known as persistent CSCR. The presence of subretinal fluid lasts

longer than 6 months and there are prolonged photoreceptor outer segments on OCT. No leakage point should be detected in the FA.

b. **Recurrent chronic:** Cases in which there is no full recovery between recurrent attacks. In recurrent chronic CSCR, an acute episode of CSCR occurs again following the complete disappearance of the subretinal fluid. Most of the patients in the recurrent remission group may begin to show recurrent chronic disease characteristics after a while. Because recurrent attacks cause permanent damage to RPE and photoreceptor cells.

4. **Chronic CSCR:** It is characterized by a serous detachment that does not regress spontaneously in 6 months, macular pooling, continued subretinal fluid accumulation in the macula, and irregular atrophic, pigmentary changes in the RPE and decrease in visual function. Other retinal changes identified in chronic CSCR are pigment migration, capillary telangiectasias, and capillary non-perfusion areas in the detached retina. In the chronic form, there are diffuse multifocal tracks of RPE atrophy. Hypofluorescence occurs in FAF due to RPE atrophy. Intraretinal cystoid degeneration can also be observed in cases lasting longer than 4-5 years.[21] There are chronic cases of CSCR accompanied by a bullous serous retinal detachment, massive exudation, and subretinal fibrin deposits.[22]

Diffuse retinal pigment epitheliopathy, a severe form of CSCR, is a rare condition that may occur. It is characterized by diffuse RPE changes, usually multifocal, irregularly distributed, with low-level leakage. Its relationship with acute CSCR has been demonstrated after long-term follow-up. Chronic CSCR is often bilateral and sometimes presents with gravitational tracts. This term is used for oblique, vertical RPE hypopigmentation areas that extend downward from the macula. Presumably, these tracts are formed by the subretinal fluid with high specific gravity collapsing down the fundus and making its way into the subretinal space. Diffuse retinal pigment epitheliopathy may extend to the periphery and cause subtotal serous retinal detachment. Foveal narrowing, cystoid macular degeneration, and chronic damage to photoreceptors are the main causes of vision loss.

Choroidal neovascularization (CNV) occurs in 2-9% of patients with chronic CSCR. Choroidal neovascularization occurs secondary to chronic leakage from the choroidal layer and inflammation in the choriocapillaris as a result of decompensation in the RPE and subsequent damage to Bruch's membrane. In CSCR, the duration of symptoms for more than 5 years and the presence of subretinal fibrosis are indicated as a sign of decreased visual function.

Pathophysiology and Risk Factors

There are many theories to determine the etiology and pathophysiology of CSCR. First, there is deterioration in the choriocapillaris and as a result, functional deterioration in the RPE occurs.[23,24] In normal healthy individuals, the fluid in the subretinal space is constantly removed from the environment, thus maintaining the adhesion and integrity between the retina and the RPE. If this integrity is lost, there will be a continuous accumulation of fluid in the subretinal space and, as a result, CSCR will develop. In some recent studies, it has been stated that the increase in the thickness of the choroidal layer in OCT may be a sign of early deterioration in the choroidal vessels and this will cause fluid accumulation in the choroidal layer, leading to serous neurosensory detachment. Disorders in the choroidal circulation and RPE are held responsible for the widely known pathophysiology of the disease. RPE detachment occurs as a result of choroidal vasodilation and increased permeability. RPE rips formed after RPE elevation burst and cause serous retinal detachment. The choriocapillaris adjacent to the choroidal vessels are thinned. In recent ultra-wide-angle imaging, vortex-vessel asymmetry and intervortex anastomoses were detected.[25,26] In addition, idiopathic CSCR patients have increased sclera thickness.[27] Scleral thickness is normal in patients with steroid-induced CSCR.[28] The thickness of the sclera also affects the response to treatment.[29]

There is no definitively defined gene for CSCR. However, 52% of patients have relatives with asymptomatic areas of RPE atrophy.[30] Choroidal thickening, pachychoroid, is found in 50% of relatives of CSCR patients.[5] Family history also appears to be a risk factor for CSCR. Complement factor H (CFH), which has a vasodilator effect on the choroid, is among the suspected molecules in the pathogenesis.[31] In other studies, it has been revealed that ARMS2 and CFH polymorphisms may be factors in the development of CSCR.[32] Gene polymorphisms encoding the Cadherin protein may also be suspected polymorphisms in the pathogenesis of CSCR.[33]

There is a relationship between CSCR and exogenous steroid use, Cushing's syndrome, organ transplantation, systemic lupus erythematosus, hypertension, sleep apnea, gastroesophageal reflux, drug use, *Helicobacter pylori* infection, and pregnancy.[34-41] Sleep disorders can cause the development of CSCR.[42,43] There is an increased risk of CSCR in the third trimester with hormonal changes during pregnancy.[34] Choroidal thickness of pregnant women increased compared to non-pregnant women.[44] This condition resolves after birth.[45] CSCR patients are at increased risk of having gastroesophageal reflux, peptic ulcer, and *Helicobacter pylori* infection.[35,36] *H. pylori*

disrupts the choroidal circulation by causing damage to the endothelial wall due to molecular mimicry.[46] Antihistamines, antibiotics, alcohol, and smoking are also risk factors for CSCR.[47] Uncontrolled hypertension and blood pressure variability are also associated with CSCR.[9,48] Although not definitively associated, there is an increase in CSCR cases in springtime.[49]

Although CSCR can also be seen in myopic eyes, hyperopia is a risk factor for CSCR.[50,51]

The effects of anxiety, corticosteroids, and epigenetic and cardiovascular risk factors on CSCR could be partially explained.[52] CSCR has been reported as a risk factor for coronary heart disease, ischemic stroke, and erectile dysfunction.[53-55] There is an increase in sympathetic-parasympathetic autonomic nervous system control towards the sympathetic nervous system.[56] Sympathomimetics, phosphodiesterase-5 inhibitors can also cause CSCR.[57,58] Although phosphodiesterase-5 (PDE-5) inhibitors (sildenafil) increase choroidal thickness, their relationship with CSCR has not been clearly demonstrated.[3,59] Considering all these conditions, it suggests that there is a systemic vascular dysfunction in the pathogenesis of CSCR disease.

Diagnosis may be more difficult in CSCR that develops secondary to steroid treatments. While steroid treatments are effective in treating many of the causes of macular edema and subretinal fluid, they cause worsening in CSCR patients. Even low-dose non-ocular steroid treatments can cause CSCR.[60] As it is known, oral and intravenous systemic corticosteroids are risk factors for the development of CSCR.[34] In addition, epidural, dermal, intranasal, intra-articular, intravaginal and periocular steroid applications have also been shown to be risk factors for CSCR.[4,34,38-41,61] A case of CSCR after intraocular administration of triamcinolone has also been reported.[4,62] CSCR cases caused by systemic steroids are mostly bilateral and atypical.[63] Steroids cause CSCR by the idiosyncratic reaction.[64] Glucocorticoids sensitize the choroidal detachment and RPE to endogenous catecholamines. In addition, glucocorticoids increase capillary fragility and permeability and cause choroidal decompensation, resulting in fluid accumulation in the subretinal area. Glucocorticoids play an important role in the regulation of choroidal blood flow by affecting nitric oxide, prostaglandin, and free radical formation. Some patients have genetically impaired RPE, and these patients develop CSCR due to the use of endogenous or exogenous cortisol. According to another hypothesis, cortisol acts directly on the RPE cells by affecting the tight junctions between them or by inhibiting the extracellular matrix components and fibroblastic activity involved in the repair process of the damaged RPE. The negative effects of cortisol use on fluid absorption in the subretinal space have been demonstrated by in vivo and in vitro electrophysiological tests.

CSCR may develop due to hormonal changes in endogenous Cushing's syndrome.[37] An increased amount of urinary cortisol was detected in half of acute CSCR cases.[65] Many studies have shown that acute and chronic CSCR is strongly associated with high cortisol levels. It has been reported that patients with acute CSCR have high cortisol levels, uses more cortisol than the control group, and the serous detachment disappears when cortisol use is discontinued. With the association of high cortisol levels with CSCR, the use of mineralocorticoid receptor antagonists in the treatment of CSCR seems to be one of the remarkable treatment modalities. Glucocorticoids bind to both glucocorticoid and mineralocorticoid receptors. With the use of aldosterone, which is a mineralocorticoid receptor agonist, dilatation and pooling occur in the choroidal vessels, and this effect is reversed with the use of mineralocorticoid receptor antagonists. This shows that glucocorticoids bind more to mineralocorticoid receptors and affect the formation of CSCR.

CSCR clinic is more common in individuals with Type A personality traits.[66] Individuals with type A personality traits have 40 times more cortisol and 4 times more epinephrine than those with type B personality traits.[67] Stress, depression, and the use of antipsychotic medication are also risk factors for CSCR.[9] Stress, somatization, depression, and narcissistic personality were frequently observed in CSCR patients.[68] Anxiolytic and antidepressant drug use is also seen in CSCR cases.[9]

The recent use of rifampin, a potent cytochrome p450 (CYP 450) enzyme activator, in patients with CSCR and the positive response to treatment raises the question of the role of these enzymes in CSCR. The cytochrome p450 enzyme is an essential enzyme responsible for the metabolism of most drugs. This enzyme is also responsible for the metabolism of endogenous substances such as cholesterol, steroids, prostaglandins, and thromboxane A2 in the body, as well as the detoxification of chemical agents. Although this enzyme is mainly found in the liver, it is also found in the lungs, intestines, kidneys, and eyes. It has been shown that the monooxygenase enzyme system dependent on cytochrome p450 is present in the RPE and ciliary body of the eye. The localization of this enzyme system in the eye indicates a relationship between endogenous steroid metabolism and CSCR.

The use of non-steroidal anti-inflammatory agents (NSAIDs) in the treatment of CSCR supports the role of prostaglandins in the pathogenesis of CSCR. In many previous studies, it has been shown that prostaglandin activity affects the retinal and choroidal circulation and this is revealed by affecting the RPE and retinal vessels.[69]

CONCLUSION

CSC is a common disease. Current theories on its pathogenesis emphasize overloading of the choroidal venous circulation. Multimodal imaging is necessary to make an accurate diagnosis. Risk factor modification is important in all patients. In particular, discontinuation of corticosteroids is necessary.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

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